(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 May 2000 (04.05.2000)

PCT

(10) International Publication Number
WO 00/24782 A3

(51) International Patent Classification[7]: C07K 19/00, C12N 15/62, 15/70, 1/21

(21) International Application Number: PCT/US99/25044

(22) International Filing Date: 25 October 1999 (25.10.1999)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/105,371 23 October 1998 (23.10.1998) US
09/428,082 22 October 1999 (22.10.1999) US

(71) Applicant: AMGEN INC. [US/US]; One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).

(72) Inventors: FEIGE, Ulrich; 3117 Deer Valley Avenue, Newbury Park, CA 91320 (US). LIU, Chuan-Fa; 1425 Clover Creek Drive, Longmont, CO 80503 (US). CHEETHAM, Janet; 1695 East Valley Road, Montecito, CA 93108 (US). BOONE, Thomas, Charles; 3010 Deer Valley Avenue, Newbury Park, CA 91320 (US).

(74) Agents: ODRE, Steven, M. et al.; Amgen, Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
6 June 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/24782 A3

(54) Title: MODIFIED PEPTIDES, COMPRISING AN FC DOMAIN, AS THERAPEUTIC AGENTS

(57) Abstract: The present invention concerns fusion of Fc domains with biologically active peptides and a process for preparing pharmaceutical agents using biologically active peptides. In this invention, pharmacologically active compounds are prepared by a process comprising: a) selecting at least one peptide that modulates the activity of a protein of interest; and b) preparing a pharmacologic agent comprising an Fc domain covalently linked to at least one amino acid of the selected peptide. Linkage to the vehicle increases the half-life of the peptide, which otherwise would be quickly degraded *in vivo*. The preferred vehicle is an Fc domain. The peptide is preferably selected by phage display, *E. coli* display, ribosome display, RNA-peptide screening, or chemical-peptide screening.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/25044

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K19/00 C12N15/62 C12N15/70 C12N1/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EMBASE, WPI Data, PAJ, EPO-Internal, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 46257 A (AMGEN INC.) 22 October 1998 (1998-10-22) page 3, line 12 -page 4, line 4 page 12, line 9 - line 25	1-3,5-7
Y	---	11-21,51
X	WO 96 18412 A (BETH ISRAEL HOSPITAL ASSOCIATION) 20 June 1996 (1996-06-20) page 8, line 14 -page 12, line 26 claims	1-3,5,6, 22-24

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 October 2000	07 12 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Nooij, F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 28828 A (AMGEN BOULDER INC.) 14 August 1997 (1997-08-14) page 5, line 23 - line 31 page 13, line 27 -page 14, line 5	1-3,5,6, 8,22-25
Y		10,11, 26-29, 34,35, 40-51
X	WO 98 24477 A (AMGEN INC.) 11 June 1998 (1998-06-11) page 10, line 31 -page 11, line 13 page 22, line 10 - line 35	1-3,5,6, 8,22-29, 35, 40-44, 46-51
X	WO 95 09917 A (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 13 April 1995 (1995-04-13) figure 3 claims	1-5, 22-24
X	WO 97 44453 A (GENENTECH INC.) 27 November 1997 (1997-11-27) examples claims	1-6, 22-24
Y		36
X	H. LOETSCHER ET AL.: "Efficacy of a chimeric TNFR-IgG fusion protein to inhibit TNF activity in animal models of septic shock." INTERNATIONAL CONGRESS SERIES, vol. 2, 1993, pages 455-462, XP002067659 Amsterdam, The Netherlands the whole document	1,2,5, 22-24
Y		37
X	B. BROCKS ET AL.: "A TNF receptor antagonistic scFv, which is not secreted in mammalian cells, is expressed as a soluble mono- and bivalent scFv derivative in insect cells." IMMUNOTECHNOLOGY, vol. 3, no. 3, October 1997 (1997-10), pages 173-184, XP002147314 Amsterdam, The Netherlands abstract figure 1	1,4-6, 22-24
Y		37
X	WO 98 31820 A (BORYUNG PHARMACEUTICAL CO. LTD.) 23 July 1998 (1998-07-23) the whole document	1-6, 22-24

-/--

INTERNATIONAL SEARCH REPORT

Inte 'ional Application No
PCT/US 99/25044

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropnate, of the relevant passages	Relevant to claim No.
Y	US 5 767 234 A (YANOFSKY ET AL.) 16 June 1998 (1998-06-16) seq.id.nos. 10,17,46,259 column 8, line 54 - line 57	10
Y	S. CWIRLA ET AL.: "Peptide agonists of the thrombopoietin receptor as potent as the natural cytokine." SCIENCE, vol. 276, no. 5319, 13 June 1997 (1997-06-13), pages 1696-1699, XP002142424 Washington, DC, USA cited in the application the whole document	18-21, 26-29, 33-37, 40-51
Y	WO 96 40772 A (JOHNSON & JOHNSON) 19 December 1996 (1996-12-19) claims 1-3 figure 9	12-17,33
A	D. JOHNSON ET AL.: "Identification of a 13 amino acid peptide mimetic of erythropoietin and description of amino acids critical for the mimetic activity of EMP1." BIOCHEMISTRY, vol. 37, no. 11, 1998, pages 3699-3710, XP002147315 Washington, DC, USA abstract tables	12-17

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional application No.
PCT/US 99/25044

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7 (partially), 8-11 (completely),
22-32 (partially), 35 (completely),
39-51 (partially)

Compositions of matter of the formula (X1)a-F1-(X2)b and multimers thereof, wherein F1 is an Fc domain, X1 and X2 are each independently selected from -(L1)c-P1, -(L1)c-P1-(L2)d-P2, -(L1)c-P1-(L2)d-P2-(L3)e-P3, and -(L1)c-P1-(L2)d-P2-(L3)e-P3-(L4)f-P4. P1, P2, P3 and P4 are each independently sequences of pharmacologically activbe peptides; L1, L2, L3 and L4 are each independently linkers, and a, b, c, d and e are each independently 0 or 1, provided that at least one of a and b is 1; DNA encoding said composition, an expression vector comprising said DNA, a host cell comprising said expression vector, Proces for preparing a pharmacologically active compound, and wherein X1 and X2 comprise an IL-1 antagonist peptide sequence.

2. Claims: 1-7 (partially), 12-17 (completely),
22-32 (partially), 33 (completely),
39-51 (partially)

As in subject 1, but wherein X1 and X2 comprise an EPO-mimetic peptide sequence.

3. Claims: 1-7 (partially), 18-21 (completely),
22-32 (partially), 34 (completely),
39-51 (partially)

As in subject 1, but wherein P1 is a TPO-mimetic peptide sequence

4. Claims: 26-32 (partially), 36 (completely),
39-51 (partially)

Process for preparing a pharmacologically active compound, which comprises selecting at least one randomized peptide that modulates the activity of a protein of interest, and preparing a pharmacologic agent comprising one Fc domain covalently linked to at least one amino acid sequence of the selected peptide(s); wherein said peptide is an MMP inhibitor peptide or a VEGF antagonist peptide.

5. Claims: 26-32 (partially), 37 (completely),

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

39-51 (partially)

As in subject 4, but wherein said peptide is a TNF antagonist peptide.

6. Claims: 26-32 (partially), 38 (completely),
39-51 (partially)

As in subject 4, but wherein said peptide is a CTLA4 mimetic peptide.

INTERNATIONAL SEARCH REPORT

ormation on patent family members

International Application No
PC, US 99/25044

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9846257 A	22-10-1998	AU 7132798 A	11-11-1998
		EP 0977583 A	09-02-2000
		ZA 9803239 A	29-10-1998
WO 9618412 A	20-06-1996	EP 0793504 A	10-09-1997
		JP 11501506 T	09-02-1999
WO 9728828 A	14-08-1997	US 6096728 A	01-08-2000
		AU 2121397 A	28-08-1997
		BR 9707325 A	13-04-1999
		CA 2244664 A	14-08-1997
		CN 1215340 A	28-04-1999
		CZ 9802373 A	15-09-1999
		EP 0904112 A	31-03-1999
		HU 9902612 A	29-11-1999
		NO 983543 A	08-10-1998
WO 9824477 A	11-06-1998	AU 5795598 A	29-06-1998
		EP 0949931 A	20-10-1999
WO 9509917 A	13-04-1995	NONE	
WO 9744453 A	27-11-1997	US 6100071 A	08-08-2000
		AU 717112 B	16-03-2000
		AU 3060497 A	09-12-1997
		EP 0907733 A	14-04-1999
		JP 2000502357 T	29-02-2000
		NZ 332779 A	29-06-1999
		US 5952199 A	14-09-1999
WO 9831820 A	23-07-1998	AU 5681498 A	07-08-1998
US 5767234 A	16-06-1998	US 5608035 A	04-03-1997
		US 5880096 A	09-03-1999
		US 5861476 A	19-01-1999
		US 5786331 A	28-07-1998
		AU 1872595 A	21-08-1995
		WO 9520973 A	10-08-1995
		ZA 9500788 A	08-02-1996
WO 9640772 A	19-12-1996	US 5767078 A	16-06-1998
		AU 6100796 A	30-12-1996
		CA 2228277 A	19-12-1996
		EP 0892812 A	27-01-1999